Brain Imaging and Behavior (2019) 13:1799–1814
https://doi.org/10.1007/s11682-019-00074-y

REVIEW ARTICLE

Chemotherapy-induced brain changes in breast cancer survivors: evaluation with multimodality magnetic resonance imaging

Yun Feng [1,2] · Xiao Dong Zhang [3] · Gang Zheng [1,4] · Long Jiang Zhang [1,5]

Published online: 1 April 2019

Abstract

Chemotherapy related cognitive impairments are common in breast cancer patients undergoing chemotherapy. These cognitive dysfunctions are mainly attributable to chemotherapy related brain structural and functional alterations. Multimodality magnetic resonance imaging (MRI) can reveal brain gray matter volume loss, white matter microstructural disruption, reduced gray matter density, impaired cerebral blood flow and brain structural and functional connection networks at both local and global levels. This review outlines the potential applications of multimodality MR imaging techniques in chemotherapy induced cognitive deficit in breast cancer survivors and provides future research perspective in this field.

Keywords Functional magnetic resonance imaging · Cognitive impairment · Breast cancer · Chemotherapy · MR imaging techniques

Abbreviations

MRI	Magnetic resonance imaging
BOLD	Blood oxygen level dependent
fMRI	Functional MRI
VBM	Voxel-based morphological
DTI	Diffusion tensor imaging
ASL	Arterial spin labeling
CRCI	Chemotherapy related cognitive impairment

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11682-019-00074-y) contains supplementary material, which is available to authorized users.

✉ Long Jiang Zhang
kevinzhlj@163.com

[1] Department of Medical Imaging, Jinling Hospital, Nanjing Medical University, Nanjing 210002, Jiangsu, China

[2] Department of Medical Imaging, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu, China

[3] Department of Radiology, Tianjin First Central Hospital, Tianjin 300192, China

[4] Monash Biomedical Imaging, Monash University, Clayton, VIC 3168, Australia

[5] Department of Medical Imaging, Jinling Hospital, Medical School of Nanjing University, 305 Zhongshan East Road, Xuanwu District, Nanjing 210002, Jiangsu Province, China

Introduction

Chemotherapy induced cognitive impairments occur in patients exposed to chemotherapeutics for non-central nervous system cancers. These patients display difficulties in attention, memory, learning ability, executive function, information processing speed and damage of visuospatial domains (Wefel et al. 2015; Tao et al. 2016; Jim et al. 2012). Neuropsychological and neuroimaging studies revealed that 8.1%–75% of breast cancer survivors showed cognitive impairment after adjuvant chemotherapy (Janelsins et al. 2011; Correa and Ahles 2007). Chemotherapy-induced neurotoxicity affects the long-term quality of life in breast cancer survivors. Most breast cancer survivor live a long and active social life after chemotherapy, these cognitive problems affect their long term quality of life. Thus, the early accurate diagnosis of chemotherapy induced cognitive impairment is crucial for guiding clinical preventive management and the later functional exercise in breast cancer survivors (Kesler et al. 2013a). However, the neural basis of chemotherapy induced cognitive impairments remains unknown, which impedes the progress of early diagnosis. Imaging is irreplaceable in detecting brain structural and functional abnormalities that underly cognition dysfunction in many diseases. In recent years, multimodality magnetic resonance imaging (MRI) such as diffusion tensor imaging (DTI), arterial spin labeling (ASL), and blood oxygen level dependent (BOLD) functional MRI (fMRI), has been widely used to

evaluate the neural mechanism of chemotherapy induced cognitive impairments in breast cancer survivors. This suite of techniques has significantly increased our understanding of the neural basis of chemotherapy induced cognitive dysfunction from both global and local brain structural and functional perspectives (Pomykala et al. 2013; Simóm et al. 2013; de Ruiter et al. 2012). This review introduces the state-of-the-art multimodality MRI techniques and their potential applications in chemotherapy-associated cognitive deficit in breast cancer survivors and provides future research perspective in this field.

Overview of multimodality MRI techniques

Many MRI techniques can be used to assess chemotherapy induced cognitive impairments in breast cancer survivors. Table 1 outlines the advatages and advantages of these MRI techniques and analysis methods.

Brain morphological imaging and data postprocessing algorithms

Although conventional anatomical MR images can provide intracranial volume information, microstructural changes are not provided. Voxel-based morphometry (VBM) can calculate the volume changes of gray matter and white matter using high-resolution structural images and quantitatively analyze the differences in the brain structure and brain tissue compositions with an a priori statistical threshold. The VBM method interrogates the individual high-resolution T1 weighted image standardized to the three-dimensional space, and then segments brain anatomy into gray matter, white matter and cerebrospinal fluid. It uses statistical parameters to test the segmentation of brain tissue components by voxel group comparison analysis, quantitatively detects brain gray and white matter density and volume, and detects abnormal brain morphology. VBM can perform whole brain analysis without the need of region of interest (ROI) as an a priori assumption, thus it is not influenced by subjective factors. However, the VBM method has some limitations, the analysis is based on spatial standardization, thus inaccurate matching of some local regions and templates will lead to systematic differences in brain morphology between groups. At the same time, due to the substantial differences in voxel content between the brain parenchyma and cerebrospinal fluid, it can produce artifacts which result in difficultly distinguishing tiny complex structural differences, such as those in the hippocampus (Good et al. 2001; Ashburner and Friston 2001).

Studies based on VBM cannot provide the direct measure of gray matter physical characteristics, such as cortical surface area, thickness and folding. Advanced brain morphological analysis present much more cortex morphological information which might become a promising tool (Wu et al. 2015). Newly developed gray matter covariance networks based on similarity-based extraction method can investiagte the large-scale structural brain network changes (Kesler et al. 2017a).

Diffusion tensor (DTI) imaging and data postprocessing algorithms

Diffusion tensor imaging (DTI) is a method for evaluating the organization of brain white matter fibers through the values of various scalar measures. It is an important breakthrough in the field of diffusion weighted imaging (DW-MRI). The common parameters used in clinical applications are fractional anisotropy (FA) and mean diffusivity (MD). FA is a sensitive and quantitative DTI parameter which is based on the detection and quantification of water molecules along nerve fibers with anisotropic Brownnian motion. MD reflects the overall diffusion level and diffusion resistance of the molecule rather than the diffusion direction. Other parameters such as axial diffusivity (AD) and radial diffusivity (RD) reflect the amount and average diffusion of different directions. Although these measures are complex, decreased FA and increased MD values reflect impaired microstructure of nerve fiber tracts (Pierpaoli et al. 1996; Basser et al. 1994), while axonal injury can lead to decreased AD value and myelin injury to increased RD value (Song et al. 2005; Budde et al. 2009). The probable mechanism of chemotherapy induced white matter impairment may be attributed to the direct neurotoxicity of the chemotherapeutic agent (Meyers 2008; Ahles and Saykin 2007), which can cross the blood-brain barrier, damage the white matter and then alter the brain pathways that transfer the information of complex cognitive tasks (Kerr et al. 1984; Engel et al. 2001).

FA is unable to differentiate changes between intra and extra-axonal diffusion. To date, advanced multishell diffusion MRI (dMRI) such as diffusion kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI) which could provide metrics from both intra and extra-axonal diffusion. Metrics of DKI can provide supplementary and additional information to DTI, while NODDI can quantify axonal dispersion and density. Higher diffusion kurtosis may indicate a restricted diffusion in cellular membranes and myelin sheaths which were associated with higher levels of white matter microstructure (Stouten-Kemperman et al. 2015). However, dMRI lacks specificity of microstructural alterations and cannot directly measure myelin. The other complementary MRI technique - myelin water imaging (MWI) has superior specifity of measures for myelin (Billiet et al. 2015). Altered diffusion parameter values may be associated with myelin sheath changes.

In recent years, many advanced post-processing methods for analyzing DTI data have been developed, such as ROI analysis, voxel-based analysis (VBA), tract-

Table 1 MRI techniques in assessing chemotherapy induced cognitive impairments in breast cancer patients

MRI techniques	Advantages	Disadvantages
MR sequences		
3D-T1	Provides high resolution anatomic information; Can be used for lesion localization, and constructing cortical network.	No functional activity can be provided.
DTI	Visualize and characterize the microstructure of white matter; sensitively quantify axonal degeneration and demyelination changes; used to construct a structural network	Partial volume effect; the "crossing fibers" issue; unable to differentiate changes between intra and extra-axonal diffusion
ASL	Measure blood flow without injection of contrast agent; provide quantitative, stable, and physiologically meaningful images	Low signal noise ratio; reduced sensitivity and increased acquisition time due to motion
BOLD-fMRI	Provide the regional and/or whole brain activation or the network topology; Biomarker for disease, monitor, monitoring therapy, studying pharmacologic efficacy, etc.; high spatial resolution and availability, noninvasive	Low temporal resolution, signal dropout/or spatial distortion at tissue interfaces between air and brain; high magnetic fields restrict flexible and complex multimodal experiments, such as concurrent EEG recording; BOLD signal reflects the indirect neurovascular BOLD signals which cannot reflect the real neuroelectric effects
Analysis algorithms		
VBM	A brain structural analysis method, calculates the volume and density changes of gray matter and white matter; evaluate the whole brain and compared directly with the original data, without the need for ROI as a priori assumptions.	Inaccurate matching of local regions and templates will lead to systematic differences in brain morphology between groups; easy to produce artifacts which result in difficult to distinguish the tiny brain structure difference.
ROI	Explores the potential activation from a whole-brain scale in complex condition designs; Sets a limited anatomical region for statistical control to increase accuracy of correction; Provides a straightforward interpretation	Creating ROI based on previous studies is used for exploration cannot for inference; Cannot reveal intrinsically connected network and their interactions; Cannot simultaneously examine multiple networks.
Graph theory	High spatial resolution and availability and suitable for a wide range of people; quantitatively analyze complex networks; maps structural and functional networks and structure function coupling in brain networks.	Low temporal resolution, signal dropout, spatial distortion; Vary statistical thresholds may affect the results; Some results are difficult to be understood
Reho	Measures local functional homogeneity of resting state fMRI signals; can detect unpredicted hemodynamic responses.	Some parameters (spatial registration, smoothing) can affect the results of ReHo; unsuitable for task-related design.
ALFF (fALFF)	Reflects the intensity of regional spontaneous brain activity in resting state fMRI; suppresses non-specific signal components; Improves the sensitivity and specificity in detecting local spontaneous brain activity.	Sensitive to the physiological noise

CRCI chemotherapy related cognitive impairment, *3D-T1* three dimensional T1 imaging, *DTI* diffusion tensor imaging, *ASL* arterial spin labeling, *VBM* voxel-based morphological, *MRI* magnetic resonance imaging, *BOLD-fMRI* blood oxygen level dependent functional MRI, *ROI* region of interest, *ICA* independent component analysis, *Reho* regional homogeneity, *ALFF* amplitude of low frequency fluctuation, *fALFF* fractional ALFF

based spatial statistics (TBSS) and graph theoretical network analysis. VBA can statistically compare whole brain FA values in the standard space voxel by voxel. TBSS solves the drawbacks of alignment and smoothing in the VBA method, which has increasingly been used in various diseases. Graph theory has also been used to construct brain white matter networks (Deprez et al. 2013). Kesler et al. (2015) used graph theory analysis to measure organization and connectivity of white matter brain networks in 34 breast cancer survivors (age range from 0.5 to 14 years). They found decreased FA in partial brain white matter regions and altered small-world connectome properties, and when removing the hub regions and edges systematically, the brain network appeared to more vulnerable to this attack due to the altered topological features.

Arterial spin labeling (ASL) imaging

Arterial spin labeling (ASL) imaging is a method of MR perfusion imaging without injection of contrast agent. It labels the water in the artery as an endogenous tracer with reverse pulses, the labeled water flows into the imaging acquisition after a certain time delay and then images are collected. In other similar conditions, the inverted pulse is not applied to collect the image again. Both sides of the image are analyzed by silhouette to obtain the cerebral blood flow (CBF) map. ASL is completely non-invasive and can be repeatedly used, and thus longitudinally follows up patients' CBF changes. There are three main categories of ASL pulse sequence: continuous ASL ($_{C}$ASL), pseudo continuous ASL ($_{PC}$ASL) and pulsed ASL ($_{P}$ASL). The $_{PC}$ASL technique is the most common choice due to the high labeling efficiency and easier

hardware implementation. Although ASL can provide quantitative, stable and physiologically meaningful CBF images (Wang et al. 2011) as a surrogate marker of metabolism (Detre et al. 2009), it also has some other problems, such as low signal to noise ratio, especially in areas with low flow velocity. Additionally, regional CBF values are often underestimated due to the transport delay effect. Motion artifact, dropout, distortion, bright spots, and labeling failure have been reported (Borogovac and Asllani 2012; Grade et al. 2015).

BOLD functional MR imaging and data postprocessing algorithms

There are two major responses to changes in neural activity which can be detected by MRI; changed local CBF and the concentration of blood oxygen. The blood oxygenation level dependent (BOLD) contrast can be detected by BOLD fMRI using a gradient refocused echo (GRE) method. The principle of BOLD can be found in other reviews (Vazquez and Noll 1998; Logothetis et al. 2001). BOLD-fMRI is non-invasive with good temporal-spatial resolution, high repeatability and is reasonably easy to perform and provides an important technique for exploring human brain function in vivo (Glover 2011). Currently, BOLD-fMRI has been widely used to explore brain activities during the resting-state and task-related states (Barkhof et al. 2014).

The typical task related fMRI experiment uses a block design or event-related design to collect MRI measures of the amplitude and timing of the hemodynamic response during different cognitive states. However, different tasks or tasks of different difficulty will lead to inconsistencies in the activation of brain regions, making the task-based different researchs lack of comparability. The resting-state functional MR imaging (rs-fMRI) evaluates the resting state (eyes closed, motionless, without thoughts) coherent brain functional connectivity and activity by measuring synchronous patterns of fluctuations in the BOLD signal. Compared with task state fMRI, rs-fMRI has the advantages of easy operation, good repeatability, and stable and reliable information (Raichle 2012; Barkhof et al. 2014). Rs-fMRI may be a particularly promising tool as a biomarker for diagnosing disease and monitoring therapy.

Many advanced rs-fMRI analysis methods have been developed to process the time series data to obtain maps of brain activation and build functional networks. These algorithms quantifying the regional intensity of individual activity include amplitude of low frequency fluctuation (ALFF) and fractional ALFF (fALFF), regional homogeneity (ReHo), while other algorithms, such as seed-based correlation analysis, independent component analysis (ICA) and graph theory which are typically used to measure internal functional network connectivity and the default mode network (DMN) (Kesler 2014).

Brain structural and functional findings

Gray matter changes

Reduced gray matter density had been widly reported after chemotherapy in breast cancer surviors. The decreased gray matter density/ volume was related to the chemotherapy induced cognitive impairement. The reductions of gray matter may be associated with chemotherapy cycles numers, and the altered right middle frontal gyrus density could mediate the chemotherapy dosage related cognitive deficit (Li et al. 2018). Decreased gray matter volume can be found as early as 1 month post chemotherapy in breast cancer survivors, indicating acute brain structural damage after chemotherapy. A prospective longitudinal neuroimaging study (McDonald et al. 2012b) enrolled a cohort of breast cancer patients that were exposed to or not exposed to chemotherapy with matched healthy controls. They first used an optimized VBM method to analyze the brain structural abnormalities in breast cancer survivors and the post-chemotherapy group demonstrated decreased frontal gray matter density. Other VBM studies also reported gray matter volume loss 1 month after chemotherapy, however the reported brain regions with volume loss were slightly different (MCdonald et al. 2010, 2012b; Lepage et al. 2014) (supplementary Tables 1 and 2). The volume loss of frontal and temporal lobes is the most consistent finding, however, volume loss of other brain regions such as cerebellum, thalamus had also been reported. It is speculated that the sample selection bias and different chemotherapy schemes such as blood–brain-barrier permeable and impermeable chemotherapeutic drugs (Seigers et al. 2013; Kesler et al. 2013b) resulted in this difference.

Many studies found the brain structural damage mediated by chemotherapy can last up to a year, then slowly recovers over time, indicating brain damage induced by chemotherapy is not persistent (McDonald et al. 2010; Lepage et al. 2014). In the longitudinal study, Lepage et al. found distributed grey matter volume reductions 1 month after chemotherapy, the altered frontal and temporal areas were partial recovery 1 year after chemotherapy. In a cross-sectional study, Inagaki et al. (Inagaki et al. 2007) found the prefrontal, parahippocampal, cingulate cortex, and precuneus regions had smaller gray matter and white matter volume in breast cancer survivors 1 year after surgery, and these regions correlated with attention, concentration and visual memory indices of cognitive impairment. However, the patients 3 years after surgery had no brain structural differences compared to the controls.

While many patients recover, long-term structural brain changes in patients with chemotherapy have also been

reported. A 10-year post chemotherapy study (de Ruiter et al. 2012) showed the parietal, occipital and cerebellar regions had reduced gray matter volume. Another large sample ($n = 184$) study found breast cancer patients 21 years after chemotherapy had smaller total brain volume and reduced gray matter volume, but there were no significant differences in the volume of white matter and hippocampus, or other local gray matter (Koppelmans et al. 2012). However, both studies were cross-sectional design except for the study of de Ruiter et al. having a non-chemotherapy group included, thus, there was no enough evidence to confirm the chemotherapy induced brain changes, the reduced total brain volume might be attributed to the effect of chemotherapy or the normal aging. Gray matter deformity was also reported (Apple et al. 2017).

Most studies did not find pre-treatment structural differences compared to healthy controls, although a few studies reported pre-treatment gray matter volume loss. McDonald et al. (McDonald et al. 2012b) observed decreased gray matter volume in the left cingulate gyrus at baseline in the patients without chemotherapy compared with healthy controls and Sato et al. (Sato et al. 2015) found pre-chemotehrapy reduced regional thalamus volume after surgery. However, these pre-treatment gray matter changes may be of uncertain significance or caused by other factors such as anesthesia. Newly developed techniques are needed to monitor the pre-treatment related possible subtle gray matter abnormities. Pre-treatment inverse relationships between structural and functional clustered connectivity (Kesler et al. 2017a) suggest a cancer-related disruption between structural and functional organizations. The similar inverse relationships between structural and functional connectome topologies were also reported in Alzheimer's disease and pervasive developmental disorder (Dai et al. 2015; Rudie et al. 2012).

Generally, the most consistent structural MRI findings are diffuse cortical and subcortical gray matter volume reductions mainly locating in the frontal and temporal lobe regions and hippocampus after chemotherapy. The acute structural damage appears 1 month after chemotherapy and partially recover after 1 year. The gray matter density/volume abnormality may be dosage related and the abnormalities in the posterior region can persist for a long time, while the frontal and temporal gray matter volume/density reductions may be transient.

White matter changes

Abnormal microstructural white mater alterations have been observed in both cross-sectional and longitudinal DTI studies. Abraham et al. (2008) conducted a cross-sectional study using ROI method and reported that DTI can detect chemotherapy-induced changes within the genu of the corpus callosum which could be related to cognitive impairment. Recently, more studies using whole-brain VBA based methods have indicated whole brain white matter lesions in breast cancer survivors were involved in cognition dysfunction. Deprez et al. (2011) studied 17 early stage breast cancer survivors 80–160 days after chemotherapy. They examined brain white matter lesions using DTI in comparison with healthy controls, and found white matter fibers in the frontal and temporal areas showed significantly decreased FA values (Fig. 1). Neuropsychological test scores of attention and processing/psychomotor speed were significantly correlated with decreased FA values in these white matter regions and increased MD in frontal white matter. They also conducted another longitudinal assessment of cognitive deficit 3 to 4 months after chemotherapy in 34 premenopausal chemotherapy women (Deprez et al. 2012), 16 chemotherapy-naive and 19 healthy controls. There were no differences between the three groups for the cognitive domains and FA value at baseline. After chemotherapy, the chemotherapy patients performed worse on attention tests, psychomotor speed, memory and showed lower FA in parietal, frontal and occipital white matter tracts than controls. Furthermore, mean regional FA changes were correlated with the cognitive dysfunctions of attention and verbal memory. These findings suggested that DTI could quantify chemotherapy induced white matter changes.

Chemotherapy induced white matter microstructural alterations can persist for a long time, a study of breast cancer survivors 10 years after high dose chemotherapy found the survivors had altered brain structure and function (de Ruiter et al. 2012). This multimodality study provides the neural substrate evidence that high dose chemotherapy may result in axonal degeneration and demyelination that persists for many years after treatment. Another series of studies included patients 20 years after chemotherapy and showed white matter and gray matter damage in adjuvant chemotherapy-treated breast cancer patients with standard dose therapy (Koppelmans et al. 2012, 2014). The above-mentioned studies are cross-sectional and other factors, such as aging may also contribute to long-term cognitive impairment in vulnerable regions (Reisberg et al. 1999). Thus, large longitudinal studies are needed to demonstrate long term damage of white mater after chemotherapy.

Evidence of recovery of white matter damage induced by chemotherapy has also been reported (Deprez et al. 2012; Billiet et al. 2018). The recovery of cognitive impairment was reported in premenopausal women who had survived breast cancer (Mcdonald et al. 2010; Lepage et al. 2014; Ahles et al. 2012). Billiet et al. conducted a 3–4 year longitudinal study in 25 young women who had undergone chemotherapy for early-stage breast cancer. They found FA values returned to baseline levels in all brain regions, with no difference compared with controls and the dMRI or MWI metrics had no significant differences between groups at 3–4 years after chemotherapy. However, this cross-sectional research with the advanced dMRI and MWI techniques cannot observe the dynamic changes of white matter microstructure which

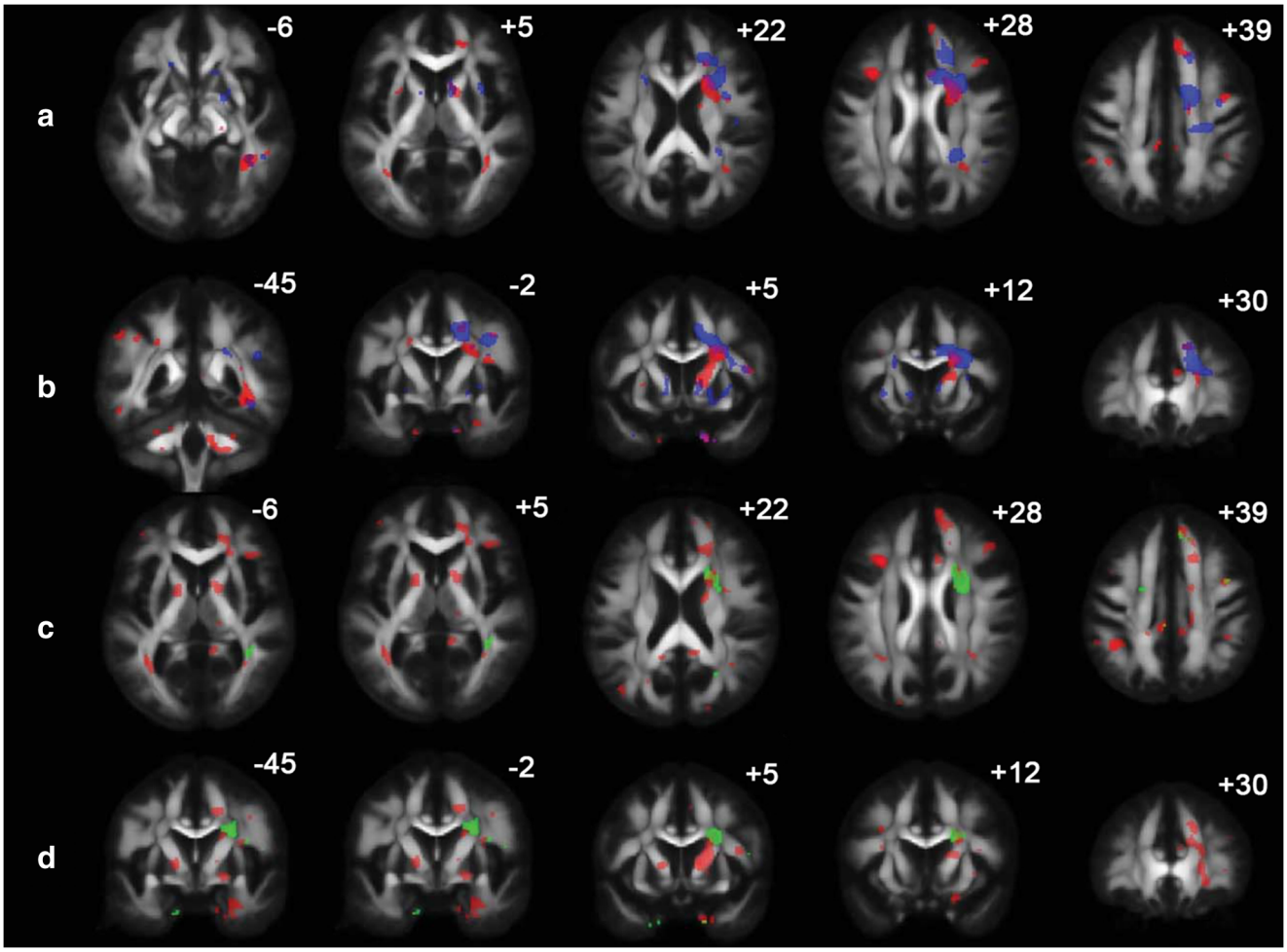

Fig. 1 Chemotherapy-induced white matter changes in breast cancer patients. a, **b** Patients undergoing chemotherapy have decreased FA (red) and increased MD (blue) compared healthy controls ($P < 0.05$). **c**, **d** Impaired patients display much lower FA value than unimpaired survivors and healthy controls. Colored red and green regions represent the impaired and the unimpaired group, respectively; colored yellow/light green regions present both effects. Numbers (mm) represent MNI coordinates for z (row a-c) and y (row b-d) axes levels, respectively. FA: fractional anisotropy; MD: mean diffusivity; MNI: Montreal Neurological Institute. With permission from Deprez et al. 2011

needed additional longitudinal study. The recovery of initially reduced white matter microstructural damage and cognitive performance observed in the young survivors provided the evidence of possible recovery, thus dynamic changes in diffusion parameters could serve as objective biological indicators for evaluating chemotherapy related cognitive impairments. They explained the recovery of white matter injury may be due to neuroplastic mechanisms, as young women would have more cognitive challenges and social activities which may contribute to partial axonal reorganization. However, this phenomenon is rarely reported in elderly patients. Older breast cancer survivors were more vulnerable to chemotherapeutic agent attack as demonstrated by lower FA values in white matter and altered structural connectomes (Kesler et al. 2015). Systemic chemotherapy may accelerate the trajectory of normal aging induced cognitive change (Ahles et al. 2012). In addition, whether age related hormone changes or chemotherapy–induced amenorrhea affect cognitive function also needs further study (Sun et al. 2012; Valentini et al. 2013; Hurria et al. 2013; Mandelblatt et al. 2014).

In conclusion, the published DTI studies have demonstrated abnormal WM DTI parameters were correlated with cognitive performance. Some WM regions may be more vulnerable to chemotherapy-induced neurotoxicity such as corpus callosum, superior and inferior longitudinal fasciculus, SFOF and corona radiate. Whereas, DTI measurement also has some limitations, such as “partial volume effect” and the “crossing fibers” issue (Deprez et al. 2013). Advanced dMRI could provide more neural substrate information from both intra and extra-axonal diffusion. These complementary techniques are sensitive to white matter changes. However, relatively few advanced dMRI and MWI-based studies have been reported in breast cancer survivors. The applications of these advanced techniques in longitudinal studies could uncover the

possible reversiblity after chemotherapy and a long-term or delayed WM damage.

Cerebral blood flow changes

Breast cancer survivors demonstrated altered resting cerebral vascular density and CBF. Two longitudinal ASL studies (Nudelman et al. 2014, 2016) found chemotherapy-induced CBF changes were complex, including both hypo-perfusion and hyper-perfusion. The increased perfusion was found in the right precentral gyrus and decreased perfusion in bilateral frontal and parietal lobes, and the group with poor baseline neuropsychological test showed higher perfusion over time. Chemotherapy-related CBF changes may be due to tissue compensation mechanisms following chemotherapy-induced damage of cells, blood vessels and tissues. The high perfusion after chemotherapy may reflect unsuccessful physiological compensation mechanism for low baseline cognitive reserve. The lower perfusion in bilateral frontal and parietal lobes was associated with decreased frontal gray mater density, whereas, the associations were not observed in the right precentral gyrus with increased perfusion. This regional dissociation between hyper-perfusion and gray matter density reduction may be due to independent functional mechanisms. CBF alterations can also be associated with chemotherapy-induced adverse effects such as chemotherapy-induced peripheral neuropathy. Breast cancer survivors with peripheral neuropathy symptoms showed higher perfusion in the anterior cingulate cortex in the resting state from baseline to 1 month (Nudelman et al. 2016) (Fig. 2), while partial recovery was observed 1 year after chemotherapy. These chemotherapy-induced CBF changes can increase the prevalence of cerebral microvascular disease (Koppelmans et al. 2015) and transient ischemic attacks (Hooning et al. 2006) when combined with radiotherapy. Further studies should focus on the correlation between the possible perfusion-structure coupling and temporal patterns of CBF recovery over time.

BOLD functional MR imaging studies

Functional connectivity

The complex human brain networks contain structural and functional connectivity. Functional connectivity evaluates the relationship between multiple rs-fMRI time series signals. It is a model of statistical dependence between neural elements (Sporns 2013). The functional connectivity between any two brain regions may be attributed to a consistent synchronous connection within or between the network (Joel et al. 2011). The most commonly used methods to examine the functional network are seed-based time series correlation algorithm, independent component analysis (ICA) and graph theory analysis (Bullmore and Sporns 2009). These analytical methods provide the possibility of detecting, analyzing and visualizing brain network architecture.

Seed-based or ROI-based connectivity

Seed-based correlation analysis is the most common and basic method for studying brain functional connectivity, which is based on extracting the BOLD time course from a ROI and calculating the temporal correlation coefficient between each voxel and the whole brain voxel (Smith et al. 2014; Joel et al. 2011). The limitation of seed-based connectivity is that it only analyzes the direct relation of interested areas, it cannot investigate other areas at the same time course; different seed regions may get different results. ROI based connectivity needs define at least two ROIs and calculates the functional connection strength (correlation) between the ROIs. Seed-based correlation is usually used to analyze the DMN. DMN is the most widely studied network because of its preferential vulnerability and sensitivity to chemotherapy. DMN reflects individual's self-examination and environmental vigilance for the resting brain. Impaired connectivity of the DMN may be an important mechanism for cognitive impairment. Using ROI-based connectivity analysis, breast cancer survivors showed reduced

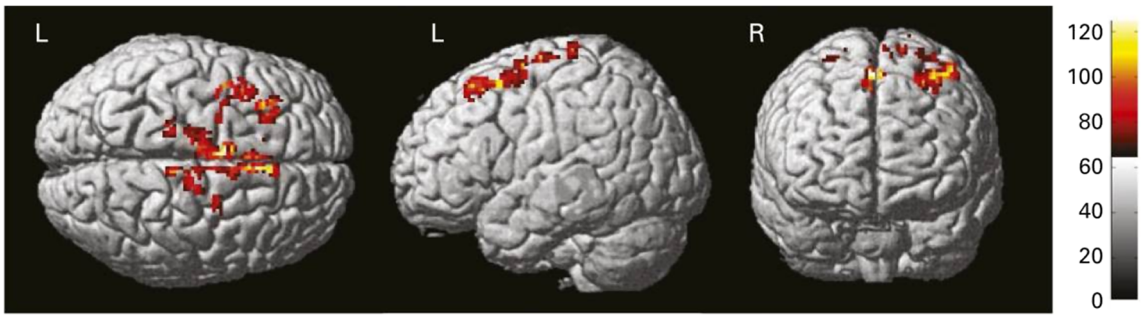

Fig. 2 Chemotherapy-related cerebral perfusion alterations. There were positive correlations between chemotherapy-induced peripheral neuropathy symptoms and cerebral perfusion in left middle and medial frontal gyri and bilateral superior frontal and cingulate gyri after chemotherapy at 1 month. The volcano scale reflects statistically significant perfusion increase as shown in the color bar. L: left: R: right. With permission from Nudelman et al. 2016

connection in the DMN after chemotherapy, especially in the cortex regions of the medial prefrontal, posterior cingulate, dorsal medial prefrontal and medial temporal lobe. This change is significantly associated with cognitive impairment (Miao et al. 2016; Dumas et al. 2013). Kesler and Blayney (2016) found patients treated with anthracycline-based chemotherapeutic agents (ANTHR) had significantly lower left precuneus connectivity with the left lateral parietal, right hippocampal, left medial frontal, right superior frontal gyrus and bilateral middle cingulate cortex compared with control groups. This study showed DMN was vulnerable to chemotherapy agents and ANTHR treatments showed more neurotoxic effects than non-ANTHR treatments (Fig. 3).

Independent component analysis based connectivity

ICA can separate the original image data into sub-datasets of different components without priori assumptions, which can identify the spatial distribution of networks in different brain regions but it cannot evaluate the correlation strength. ICA can effectively detect the unexpected activation areas that seed-based correlation cannot obtain (Lee et al. 2013; Joel et al. 2011). It can simultaneously examine multiple networks (Zhang et al. 2014), such as the DMN, dorsal attention network, salience network, frontal control network and sensory motor network. Hampson et al. (2015) used ICA to evaluate functional connectivity in breast cancer survivors with persistent fatigue. They found fatigued survivors showed significantly greater connectivity mainly between left inferior parietal lobule to right superior frontal gyrus. The connectivity correlation strength between these areas was related to survivors′ physical fatigue and sleep issues. The positive correlation between the DMN and the superior frontal gyrus in the persistent fatigue patients was not observed in non-fatigued patients. These results showed that DMN, especially superior frontal gyrus and the medial prefrontal cortex were key regions in response to chemotherapy-related physical fatigue.

Graph theory analysis based connectivity

Graph theory analysis has been widely used in rs-fMRI research. Based on graph theory, the human brain is a highly complex and efficient transmission network with many important topological properties, such as “small world” property, modular organization structure and core brain area (Bullmore and Sporns 2009; Boccaletti et al. 2006). A complex network can be depicted as a graph of edges and nodes. Parameters of graph theory analysis could quantify the complex networks (Table 2). The normal brain network exhibits a “small world” nature with high network efficiency, optimized

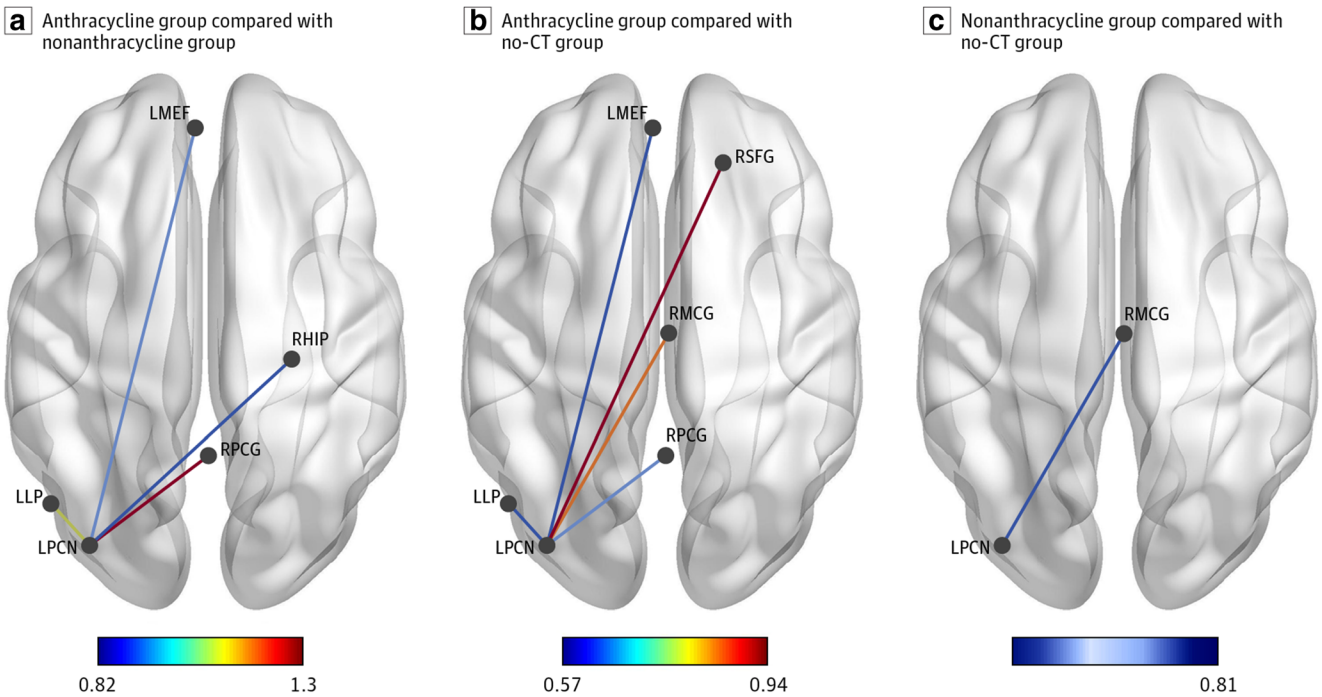

Fig. 3 Chemotherapy induced default mode network (DMN) connectivity changes following different chemotherapy regimens. a Breast cancer patients treated with anthracycline (ANTHR) had lower brain functional connections between the LPCN and other DMN subnetwork areas compared with non-ANTHR therapy patients. **b** Patients treated with anthracycline demonstrated the same altered connectivity between LPCN and other networks compared with the patients did not receive any chemotherapy. **c** The nonanthracycline agent treated patients indicated decreased functional connectivity between LPCN and RMCG compared with no-chemotherapy patients. Color bars show connection strength. LPCN: left precuneus; LMEF: left medial frontal; LLP: left lateral parietal; RHIP: right hippocampus; RPCG: right posterior cingulate; RSFG: right superior frontal gyrus. With permission from Kesler et al. 2015

Table 2 Graph theory measures in brain networks

Major network metrics	Definition	Comments
Node degree	The number of edges directly connected to a given node	The higher degree of the node, the more connections the node has.
Degree distribution	The degrees of all the network's nodes	Networks with different distribution will exhibit different network behaviors during network attacks.
Clustering coefficient	Measures the number of directly connections that exist between the nearest neighbours and a node	Measure the degree of network collectivization.
Local efficiency	Local efficiency is the average of the local efficiencies of all nodes	Measure the network local information transmission capability.
Global efficiency	Measures the global transmission capacity of the network.	The shorter the shortest path of the node, the higher the global efficiency of the network.
Shortest path length	The path with the fewest edges between two nodes	The shortest path can transfer information faster.
Centrality	A statistical index describing the role and status of nodes in a network	Centrality is important to efficient communication.
Hub	Nodes with high degree or centrality	High degree or centrality is crucial to efficient communication.
Module	A group of nodes with dense internal connections but sparse external connections in the network	The modular structure allows modules with different functions to evolve relatively independently without affecting other modules.

connection structure and high topological stability. The complex networks have relatively high local and global efficiency in information processing and transmission. Recently, researchers used graph theory to analyze complex brain networks after chemotherapy. These studies provided powerful evidence that chemotherapy related cognitive deficits are associated with abnormal topological changes from large scale structure and function perspectives (Hosseini et al. 2012; Kesler et al. 2017a; Bruno et al. 2012; Piccirillo et al. 2015).

It has been reported breast cancer survivors with accepting chemotherapeutic agents had decreased transfer efficiency of neural network. Bruno et al. (2012) examined the brain network in breast cancer patients 5 years after therapy using graph theory. They found that survivors showed decreased global clustering values, reduced path length and small-wordlness in frontal, temoral and striatal regions. The regulation networks of executive, memory and emotion displayed altered nodal degree and hub numbers. This functional brain network research illuminated that chemotherapy related cognitive deficit may act via disrupted coordination between global and regional networks. Structural network studies also showed decreased clustering coefficient and small-world properties in the gray matter network or white matter network compared to controls (Kesler et al. 2015; Hosseini et al. 2012). Damaged memory and executive functioning can be related to the frontotemporal regions with lower interactive nodes and decreased degree centrality. These large-scale complex brain network studies based on graph theory analysis revealed the functional network alterations following chemotherapy in breast cancer survivors, providing a neurobiological basis for chemotherapy induced cognitive impairment.

Task related activation

Task-based fMRI is sensitive to changes in brain activity. Many studies have shown that patients receiving chemotherapy had increased brain activity (Ferguson et al. 2007; Kesler et al. 2009; Menning et al. 2015) or reduced brain activity (de Ruiter et al. 2011; Deprez et al. 2014; Kesler et al. 2013a; Cimprich et al. 2010; Pomykala et al. 2013; López Zunini et al. 2013) after chemotherapy. Most prospective (McDonald et al. 2012a; López Zunini et al. 2013) and cross-sectional fMRI studies demonstrated decreased activation in the left anterior cingulate cortex and the regions around the left inferior frontal gyrus which may be due to dysregulation of the higher attentional demands in multitasking after chemotherapy. McDonald et al. (2012a) reported lower levels of brain activation when the patients were performing a memory task after chemotherapy. The decreased activation in inferior frontal regions may be contributed to chemotherapy induced brain function impairment that cannot maintain the baseline hyperactivation status. There were also some different findings after chemotherapy, for example, hyperactivation in brain regions such as the prefrontal cortex were observed (Ferguson et al. 2007; Menning et al. 2015, 2017). They explained that increased activity may represent a compensation for dysfunction by recruiting a broader neural network. The inconsistent activation between these studies is likely related to the difficulty levels of the task after controlling for other covariates. Difficult tasks will lead to low levels of brain activity, while a relatively simple task will enable brain activity to increase to the baseline level. This difference requires researchers to develop a number of cognitive tasks

that match the study population demographics, so that the cognitive tasks would be relatively equivalent and the results among different research groups would be more comparable.

Importantly, baseline levels will have an important effect on the study results. Some studies reported baseline cognitive changes before chemotherapy. Baseline functional brain activation pattern differences were found in verbal memory retrieval, visuospatial working memory and selective attention in post-chemotherapy survivors compared to healthy controls (McDonald et al. 2012a; López Zunini et al. 2013; Cimprich et al. 2010; Scherling et al. 2011, 2012). These findings suggested cancer-related factors may contribute to cognitive deficit. Pretreatment hyperactivation was thought to be a compensation effect of cancer-related cognitive impairment. However, no significant neural activation differences before treatment were also reported compared with controls (Deprez et al. 2014) (Fig. 4). They interpreted that the difference from other studies was due to enrolling younger women who may have higher baseline cognitive reserves. Other pretreatment risk factors – physical and psychological distress (worry, anxiety, depression, fatigue, and sleep problems) also exhibit altered brain BOLD signals (Churchill et al. 2015; Cimprich et al. 2010; Berman et al. 2014; Menning et al. 2015), higher worry and lower fatigue were associated with lower brain deactivation and decreased cognitive performance (Berman et al. 2014; Cimprich et al. 2010). These pretreatment differences emphasize the need to understand the effects of confounding variables when considering the effect of post-treatment measures (Jung et al. 2017; Kesler et al. 2017b).

Partial recovery of functional connectivity (Dumas et al. 2013) and task related activation (McDonald et al. 2012a) were observed in the dorsal attention network and the inferior frontal regions which partially returned to baseline level 1 year later. These altered areas were also reported in gray and white matter changes after chemotehrapy. The pretreatment and one-year post-chemotherapy hyperactivation in breast cancer patients may reflect increased recruitment of expanded neural circuitry to support structural functioning (McDonald et al. 2012b). However, later-onset cognitive changes and persistent cognitive deficits are also reported that vary by age, chemotherapy dose, chemotherapeutic agent, treatment stage, cognitive function studied and comparison groups (Jung et al. 2017; de Ruiter et al. 2011; Kesler et al. 2011). Thus, the recovery to a baseline levels which may reflect the compensation ability improvements with time in some degree, it is not the back to normal level and some brain function abnormality may persist for a long time.

Resting state spontaneous brain activity

ALFF uses the amplitude of a specific low frequency range (0.01~0.08 Hz) BOLD signal to reflect the amplitude or intensity of spontaneous activity of each neuron voxel, so as to observe the change of regional brain activity directly (Zang et al. 2007). fALFF, is the ratio of the power of the low-frequency range to the power of the whole frequency range and can effectively reduce the influence of noise within the ventricular system and vascular lacuna, to improve the sensitivity and specificity of measures of the brain resting state network (Zou et al. 2008). ReHo uses the Kendall's coefficient concordance to calculate the local homogeneity of a given voxel and its neighborhood in a voxel-wise way (Zang et al. 2004). The ReHo method considers both the local neighborhood information and the time course information. ReHo analysis can detect unpredicted hemodynamic responses and explores the inhomogeneity of the human brain function (Jiang and Zuo 2016). ALLF and ReHO have been widely used in in

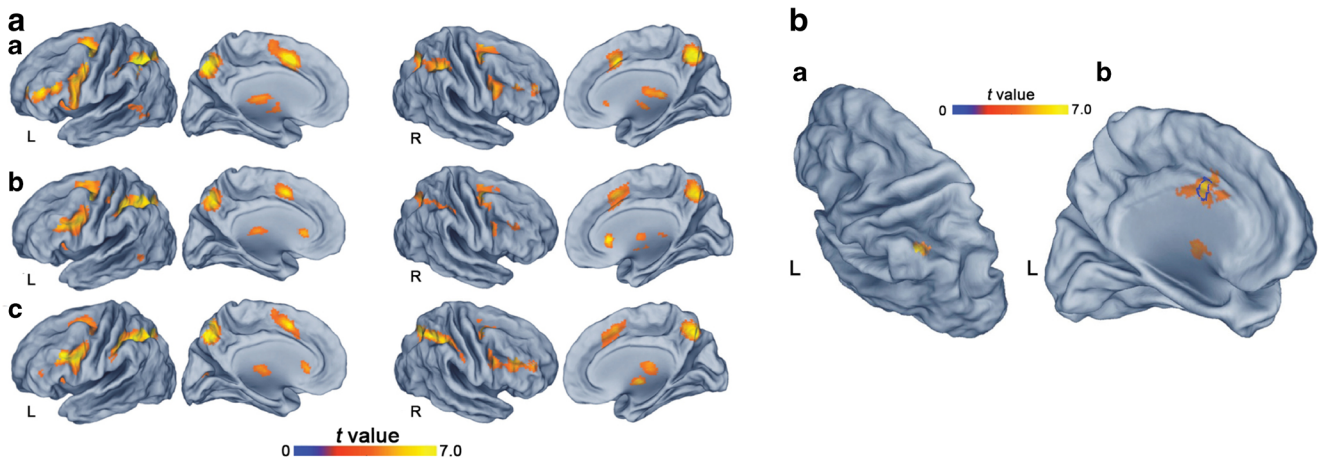

Fig. 4 Longitudinal assessment of task related activation task related activation. At baseline, the three groups (A, B, C) showed no different activation in the colored brain regions with multitasking (**a**). After chemotherapy, breast cancer patients demonstrated decreased activation in the left anterior cingulate cortex and intraparietal sulcus during multimasking compared with baseline (**b**). A, patients plan to receive chemotherapy, B, patients do not receive chemotherapy, C, healthy controls. L: left; R: right. With permission from Deprez et al. 2014

hepatic encephalopathy (Zhang and Zhang 2018). However, relatively few studies have been reported in the field of chemotherapy induced cognitive dysfunction. Mo et al. (2017) detected extensively altered ReHO values in cerebellum, orbitofrontal area, temporal gyrus and prefrontal cortex 2 or 3 weeks after chemotherapy, thus they concluded ReHo could be used to detect the short-term brain function changes.

In conclusion, functional brain activation and connectivity alterations were found both pre-treatment and post-treatment (de Ruiter and Schagen 2013). Functional MR techniques were sensitive to measure subtle brain changes, revealing the changed activation in the posterior cingulate cortex, frontal lobe, temporal lobe and altered connections in dorsal attention network and DMN. The inconsitst brain activation before and after chemotherapy may also reflect brain's compensatory ability. Cancer or treatment induced physical and psychological distress may accelerate or aggravate these cognitive dysfunctions. Similar to the structural recovery pattern, most reported brain function partial recovery was observed 1 year after chemotherapy, however, some brain alterations seemed irreversible for a long time.

Multimodality MRI methods

Multimodal MR imaging studies with the combination of rs-fMRI, DTI, VBM and other MRI techniques such as MR spectroscopy (MRS) can provide a more comprehensive assessment of functional, structural, and metabolic changes within the brain. They allow correlations between them, shedding light on the understanding of the neurobiological mechanism of chemotherapy induced cognitive deficit (de Ruiter et al. 2012; McDonald et al. 2012b; Menning et al. 2015; Conroy et al. 2013; Nudelman et al. 2014; Kesler et al. 2017a; Mo et al. 2017). De Ruiter et al. used DTI, single voxel proton MR spectroscopy (1H-MRS) and VBM to evaluate the neural substrates underlying cognitive deficits in breast cancer survivors. They found the higher MD value in posterior parietal area was associated with lower gray matter volume and fMRI hypoactivation. The DTI parameters were negatively related to N-acetylaspartate (NAA) and NAA/Cr in the chemotherapy group. Combining brain functional and structural connectivity study suggests that brain structure has the ability to stabilize and support dynamic brain function networks, altered brain structure breaks the balance between brain structure and function (Kesler et al. 2017a). MR perfusion imaging combined VBM (Nudelman et al. 2014) and rs-fMRI combined DTI (Mo et al. 2017) studies provide more comprehensive overview on relationships between chemotherapy or cancer related structural and functional changes. These studies provide the evidences to support the use of multimodal MR imaging to study in vivo pathophysiological basis of chemotherapeutic drugs and neurotoxicity. Thus, multimodal MR imaging studies should be advocated in this field.

Considerations for neuroimaging findings

Both structural and functional MRI studies have observed the chemotherapy related brain alterations (Fig. 5). These functional and structural damage areas were partially overlaped. Pre-treatment structural abnormalities were rarely reported and thus the effects are likely subtle and limited, while brain functional alterations are found both pre-treatment and post-treatment. Both brain functional and structural recovery pattern seems to follow the similar dynamic process. The acute brain damage appears 1 month after chemotherapy and partial recovery after 1 year. However, gray matter abnormalities after chemotherapy (< 1 month) (Li et al. 2018; McDonald et al. 2010) seems appear earlier than white matter microstructural damage (about 3 months) (Billiet et al. 2018; Deprez et al. 2012).

The development of chemotherapy brain is complex, other pre–treatment factors such as the tumor related inflammation, oxidative stress, DNA damage, susceptibility gene; pretreatment patients' conditions such as physical and psychological distress (worry, anxiety, depression, fatigue, sleep problems); post-treatment factors such as cellular neural toxicity of chemotherapeutic drugs, combined endocrine or radiotherapy, age-related neural degeneration. All these risk factors will accelerate or aggravate this process. Thus, we need weight the effects of all confounding variables in performing chemotherapy induced brain damage.

Different types of chemotherapeutic agents may have different impacts (Kesler and Blayney 2016). The diversity of chemotherapy drugs, therapeutic doses (Collins et al. 2013) and individual response may have different effects on cognitive impairments (Supplementary Tables 1 and 2). Breast cancer survivors treated with adjuvant fluorouracil (CMF, cyclophosphamide, methotrexate and fluorouracil) chemotherapy had significantly worse memory, processing speed and executive function after 20 years (Koppelmans et al. 2015). Some breast cancer patients may be more sensitive to the standard ANTHR and/or taxane (Piccirillo et al. 2015).

Perspectives

Although many advances have been obtained in the MR imaging filed of chemotherapy induced cognitive deficit, many issues remain to be further resolved. Structural and functional neuroimaging techniques provide information on CBF, metabolism, and complex brain networks which can examine the neural basis of cancer or treatment-related cognitive impairment. However, there are some

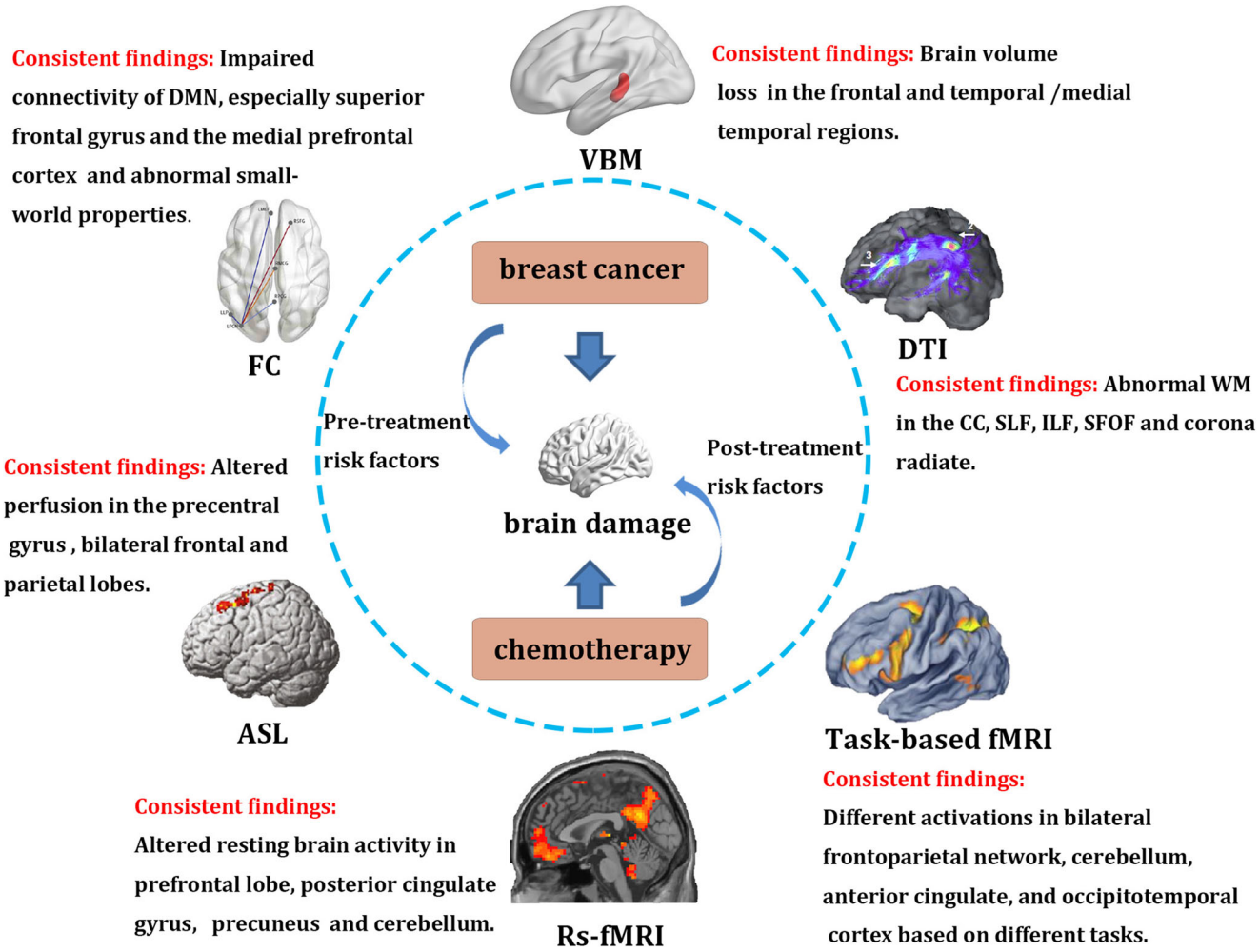

Fig. 5 Summary of structural and functional MRI studies on chemotherapy related brain alterations in patients with breast cancer. VBM: voxel-based morphological, FC: functional connectivity, DTI: diffusion tensor imaging, Rs-fMRI: rest state functional MRI, ASL: arterial spin labeling, DMN: default mode network, CC: corpus callosum, SLF: superior longitudinal fasciculus, ILF: inferior longitudinal fasciculus, SFOF: superior fronto-occipital fasciculus

inconsistent results between studies with the same imaging modalities which could be partly attributed to differences in cognitive tasks, chemotherapy regimens, population characteristics, image processing methods and individual variance. In the future, the development of a standardized neurocognitive assessment (brain morphology imaging, functional imaging, neuropsychological tests, etc.) criterias may serve as useful adjunct tools for clinical diagnosis and monitoring cog nitive impairment. The International Cognition and Cancer Task Force (ICCTF) offers recommendations for neuroimaging methodological approach and clinical, cognitive and biomarker data colletion (Deprez et al. 2018), which will have a positive effect on the related study in future.

Future work should focus on chemotherapy susceptible brain regions, damaged brain recovery time and patterns, and persistent damaged regions which require medication and rehabilitation training intervention. There may be a link between genotype diversity, cancer and treatment, cognitive impairment and damaged brain areas. Research progress from other diseases such as mild cognitive impairment or Alzheimer disease can shed the light for uncovering the neuropathological mechanism of chemotherapy induced brain damage. Neuroimaging combined with genetics and molecular biology will probably reveal the neuro-pathophysiology mechanism of chemotherapy induced-brain changes. The state-of-the-art multimodality MR imaging/positron emission tomography (PET) can play a key role in this setting. Additionally, prospective, longitudinal, multicenter studies are urgently needed to focus on important scientific issues in the field of chemotherapy induced brain changes using advanced multimodality MR imaging.

Machine learning has brought opportunities and challenges to the development of biological research (Rick et al. 2018; Koch 2018). With the machine learning for the pre-treatment

cytokines (Henneghan et al. 2018) and resting state fMRI connectome metrics (Kesler et al. 2017b), researchers found that cytokines were more important predictors of chemotherapy related cognitive impairment, and specific cytokines may link the specific cognitions. Machine learning is a promising tool for improving the diagnosis of early cognitive impairment and predicting the progression of chemotherapy induced brain changes.

Conclusions

A large number of MRI-based studies show abnormal structural and functional brain alterations after chemotherapy in breast cancer survivors. However, controversy still exists, such as the recovery of damaged brain after chemotherapy and baseline brain functional changes. Prospective multicenter, multivariate, multimodal MR imaging studies are needed to elucidate the potential mechanisms of chemotherapy-associated cognitive disorders. This will further improve the patient care post-chemotherapy, including the development of targeted therapies, preventative strategies and cognitive rehabilitation treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent This is a review article and therefore does not contain any new data from studies with human participants or animals performed by any of the authors.

References

Abraham, J., Haut, M. W., Moran, M. T., Filburn, S., Lemiuex, S., & Kuwabara, H. (2008). Adjuvant chemotherapy for breast cancer: effects on cerebral white matter seen in diffusion tensor imaging. *Clinical Breast Cancer, 8*, 88–91. https://doi.org/10.3816/CBC.2008.n.007.

Ahles, T. A., & Saykin, A. J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature Reviews. Cancer, 7*, 192–201. https://doi.org/10.1038/nrc2073.

Ahles, T. A., Root, J. C., & Ryan, E. L. (2012). Cancer- and cancer treatment–associated cognitive change: an update on the state of the science. *Journal of Clinical Oncology, 30*, 3675–3686. https://doi.org/10.1200/JCO.2012.43.0116.

Apple, A. C., Ryals, A. J., Alpert, K. I., Wagner, L. I., Shih, P. A., Dokucu, M., et al. (2017). Subtle hippocampal deformities in breast cancer survivors with reduced episodic memory and self-reported cognitive concerns. *Neuroimage Clinical, 14*(C), 685–691. https://doi.org/10.1016/j.nicl.2017.03.004.

Ashburner, J., & Friston, K. J. (2001). Why voxel-based morphometry should be used. *Neuroimage, 14*, 1238–1243. https://doi.org/10.1006/nimg.2001.0961.

Barkhof, F., Haller, S., & Rombouts, S. A. (2014). Resting-state functional MR imaging: a new window to the brain. *Radiology, 272*, 29–49. https://doi.org/10.1148/radiol.14132388.

Basser, P. J., Mattiello, J., & Lebihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal, 66*, 259–267. https://doi.org/10.1016/S0006-3495(94)80775-1.

Berman, M. G., Askren, M. K., Jung, M., Therrien, B., Peltier, S., Noll, D. C., Zhang, M., Ossher, L., Hayes, D. F., Reuter-Lorenz, P. A., & Cimprich, B. (2014). Pretreatment worry and neurocognitive responses in women with breast cancer. *Health Psychology, 33*, 222–231. https://doi.org/10.1037/a0033425.

Billiet, T., Vandenbulcke, M., Mädler, B., Peeters, R., Dhollander, T., Zhang, H., Deprez, S., van den Bergh, B. R. H., Sunaert, S., & Emsell, L. (2015). Age-related microstructural differences quantified using myelin water imaging and advanced diffusion MRI. *Neurobiology of Aging, 36*(6), 2107–2121. https://doi.org/10.1016/j.neurobiolaging.2015.02.029.

Billiet, T., Emsell, L., Vandenbulcke, M., Peeters, R., Christiaens, D., Leemans, A., van Hecke, W., Smeets, A., Amant, F., Sunaert, S., & Deprez, S. (2018). Recovery from chemotherapy-induced white matter changes in young breast cancer survivors. *Brain Imaging and Behavior, 12*, 64–77. https://doi.org/10.1007/s11682-016-9665-8.

Boccaletti, S., Latora, V., Moreno, Y., Chavez, M., & Hwang, D. U. (2006). Complex networks: structure and dynamics. *Physics Reports, 424*, 175–308. https://doi.org/10.1016/j.physrep.2005.10.009.

Borogovac, A., & Asllani, I. (2012). Arterial spin labeling (ASL) fMRI: advantages, theoretical constrains, and experimental challenges in neurosciences. *International Journal of Biomedical Imaging, 2012*, 818456. https://doi.org/10.1155/2012/818456.

Bruno, J., Hosseini, S. M., & Kesler, S. (2012). Altered resting state functional brain network topology in chemotherapy-treated breast cancer survivors. *Neurobiology of Disease, 48*, 329–338. https://doi.org/10.1016/j.nbd.2012.07.009.

Budde, M. D., Xie, M., Cross, A. H., & Song, S. K. (2009). Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: a quantitative pixelwise analysis. *The Journal of Neuroscience, 29*, 2805–2813. https://doi.org/10.1523/JNEUROSCI.4605-08.2009.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience, 10*, 186–198. https://doi.org/10.1038/nrn2575.

Churchill, N. W., Cimprich, B., Askren, M. K., Reuter-Lorenz, P. A., Jung, M. S., Peltier, S., et al. (2015). Scale-free brain dynamics under physical and psychological distress: Pre-treatment effects in women diagnosed with breast cancer. *Human Brain Mapping, 36*, 1077–1092. https://doi.org/10.1002/hbm.22687.

Cimprich, B., Reuter-Lorenz, P., Nelson, J., Clark, P. M., Therrien, B., Normolle, D., Berman, M. G., Hayes, D. F., Noll, D. C., Peltier, S., & Welsh, R. C. (2010). Prechemotherapy alterations in brain function in women with breast cancer. *Journal of Clinical and Experimental Neuropsychology, 32*, 324–331. https://doi.org/10.1080/13803390903032537.

Collins, B., MacKenzie, J., Tasca, G. A., Scherling, C., & Smith, A. (2013). Cognitive effects of chemotherapy in breast cancer patients: a dose response study. *Psycho-oncology, 22*, 1517–1527. https://doi.org/10.1002/pon.3163.

Conroy, S. K., McDonald, B. C., Smith, D. J., Moser, L. R., West, J. D., Kamendulis, L. M., Klaunig, J. E., Champion, V. L., Unverzagt, F. W., & Saykin, A. J. (2013). Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. *Breast Cancer Research and Treatment, 137*, 493–502. https://doi.org/10.1007/s10549-012-2385-x.

Correa, D. D., & Ahles, T. A. (2007). Cognitive adverse effects of chemotherapy in breast cancer patients. *Current Opinion in Supportive and Palliative Care, 1*, 57–62. https://doi.org/10.1097/SPC.0b013e32813a328f.

Dai, Z., Yan, C., Li, K., Wang, Z., Wang, J., Cao, et al. (2015). Identifying and mapping connectivity patterns of brain network hubs in Alzheimer's disease. *Cerebral Cortex, 25*, 3723–3742. https://doi.org/10.1093/cercor/bhu246.

de Ruiter, M. B., & Schagen, S. B. (2013). Functional MRI studies in non-CNS cancers. *Brain Imaging and Behavior, 7*(4), 388–408. https://doi.org/10.1007/s11682-013-9249-9.

de Ruiter, M. B., Reneman, L., Boogerd, W., Veltman, D. J., van Dam, F. S., Nederveen, A. J., et al. (2011). Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Human Brain Mapping, 32*, 1206–1219. https://doi.org/10.1002/hbm.21102.

de Ruiter, M. B., Reneman, L., Boogerd, W., Veltman, D. J., Caan, M., Douaud, G., Lavini, C., Linn, S. C., Boven, E., van Dam, F. S. A. M., & Schagen, S. B. (2012). Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging. *Human Brain Mapping, 33*, 2971–2983. https://doi.org/10.1002/hbm.21422.

Deprez, S., Amant, F., Yigit, R., Porke, K., Verhoeven, J., Van den Stock, J., et al. (2011). Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. *Human Brain Mapping, 32*, 480–493. https://doi.org/10.1002/hbm.21033.

Deprez, S., Amant, F., Smeets, A., Peeters, R., Leemans, A., Van Hecke, W., et al. (2012). Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. *Journal of Clinical Oncology, 30*, 274–281. https://doi.org/10.1200/JCO.2011.36.8571.

Deprez, S., Billiet, T., Sunaert, S., & Leemans, A. (2013). Diffusion tensor MRI of chemotherapy-induced cognitive impairment in non-CNS cancer patients: a review. *Brain Imaging and Behavior, 7*, 409–435. https://doi.org/10.1007/s11682-012-9220-1.

Deprez, S., Vandenbulcke, M., Peeters, R., Emsell, L., Smeets, A., Christiaens, M. R., Amant, F., et al. (2014). Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints. *Journal of Clinical Oncology, 32*, 2031–2038. https://doi.org/10.1200/JCO.2013.53.6219.

Deprez, S., Kesler, S. R., Saykin, A. J., Silveman, D. H., de Ruiter, M. B., & McDonald, B. C. (2018). International cognition and cancer task force recommendations for neuroimaging methods in the study of cognitive impairment in non-CNS cancer patients. *Journal of the National Cancer Institute, 110*(3), 223–231. https://doi.org/10.1093/jnci/djx285.

Detre, J. A., Wang, J., Wang, Z., & and Rao, H. (2009). Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. Current Opinion in Neurology 22, 348–355. doi: https://doi.org/10.1097/WCO.0b013e32832d9505.

Dumas, J. A., Makarewicz, J., Schaubhut, G. J., Devins, R., Albert, K., Dittus, K., & Newhouse, P. A. (2013). Chemotherapy altered brain functional connectivity in women with breast cancer: a pilot study. *Brain Imaging and Behavior, 7*, 524–532. https://doi.org/10.1007/s11682-013-9244-1.

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Reviews. Neuroscience, 2*, 704–716. https://doi.org/10.1038/35094565.

Ferguson, R. J., McDonald, B. C., Saykin, A. J., & Ahles, T. A. (2007). Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. *Journal of Clinical Oncology, 25*, 3866–3870. https://doi.org/10.1200/JCO.2007.10.8639.

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics of North America, 22*, 133–139vii. https://doi.org/10.1016/j.nec.2010.11.001.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage., 14*, 21–36. https://doi.org/10.1006/nimg.2001.0786.

Grade, M., Hernandez Tamames, J. A., Pizzini, F. B., Achten, E., Golay, X., & Smits, M. A. (2015). neuroradiologist's guide to arterial spin labeling MRI in clinical practice. *Neuroradiology, 57*, 1181–1202. https://doi.org/10.1007/s00234-015-1571-z.

Hampson, J. P., Zick, S. M., Khabir, T., Wright, B. D., & Harris, R. E. (2015). Altered resting brain connectivity in persistent cancer related fatigue. *Neuroimage Clinical, 7*(8), 305–313. https://doi.org/10.1016/j.nicl.2015.04.022.

Henneghan, A. M., Palesh, O., Harrison, M., & Kesler, S. R. (2018). Identifying cytokine predictors of cognitive functioning in breast cancer survivors up to 10 years post chemotherapy using machine learning. *Journal of Neuroimmunology, 320*, 38–47. https://doi.org/10.1016/j.jneuroim.2018.04.012.

Hooning, M. J., Dorresteijn, L. D., Aleman, B. M., Kappelle, A. C., Klijn, J. G., Boogerd, W., et al. (2006). Decreased risk of stroke among 10-year survivors of breast cancer. *Journal of Clinical Oncology, 24*, 5388–5394.

Hosseini, S. M., Della, K., & Kesle, S. R. (2012). Altered small-world properties of gray matter networks in breast cancer. *BMC Neurology, 12*, 28. https://doi.org/10.1186/1471-2377-12-28.

Hurria, A., Patel, S. K., Mortimer, J., Luu, T., Somlo, G., Katheria, V., Ramani, R., Hansen, K., Feng, T., Chuang, C., Geist, C. L., & Silverman, D. H. S. (2013). The effect of aromatase inhibition on the cognitive function of older patients with breast cancer. *Clinical Breast Cancer, 14*, 132–140. https://doi.org/10.1016/j.clbc.2013.10.010.

Inagaki, M., Yoshikawa, E., Matsuoka, Y., Sugawara, Y., Nakano, T., Akechi, T., Wada, N., Imoto, S., Murakami, K., Uchitomi, Y., & and The Breast Cancer Survivors' Brain MRI Database Group. (2007). Smaller regional volumes of gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer, 109*, 146–156. https://doi.org/10.1002/cncr.22368.

Janelsins, M. C., Kohli, S., Mohile, S. G., Usuki, K., Ahles, T. A., & Morrow, G. R. (2011). An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Seminars in Oncology, 38*, 431–438. https://doi.org/10.1053/j.seminoncol.2011.03.014.

Jiang, L., & Zuo, X. N. (2016). Regional homogeneity: a multimodal, multiscale neuroimaging marker of the human connectome. *Neuroscientist., 22*, 486–505. https://doi.org/10.1177/1073858415595004.

Jim, H. S. L., Phillips, K. M., Chait, S., Faul, L. A., Popa, M. A., Lee, Y. H., Hussin, M. G., Jacobsen, P. B., & Small, B. J. (2012). Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *Journal of Clinical Oncology, 30*, 3578–3587. https://doi.org/10.1200/JCO.2011.39.5640.

Joel, S. E., Caffo, B. S., van Zijl, P. C., & Pekar, J. J. (2011). On the relationship between seed-based and ICA-based measures of functional connectivity. *Magnetic Resonance in Medicine, 66*, 644–657. https://doi.org/10.1002/mrm.22818.

Jung, M. S., Zhang, M., Askren, M. K., Berman, M. G., Peltier, S., Hayes, D. F., Therrien, B., Reuter-Lorenz, P. A., & Cimprich, B. (2017). Cognitive dysfunction and symptom burden in women treated for breast cancer: a prospective behavioral and fMRI analysis. *Brain Imaging and Behavior, 11*, 86–97. https://doi.org/10.1007/s11682-016-9507-8.

Kerr, I. G., Zimm, S., Collins, J. M., O'Neill, D., & Poplack, D. G. (1984). Effect of intravenous dose and schedule on cerebrospinal fluid

pharmacokinetics of 5-fluorouracil in the monkey. *Cancer Research, 44*, 4929–4932.

Kesler, S. R. (2014). Default mode network as a potential biomarker of chemotherapy-related brain injury. *Neurobiology of Aging, 35*(Suppl 2), S11–S19. https://doi.org/10.1016/j.neurobiolaging.2014.03.036.

Kesler, S. R., & Blayney, D. W. (2016). Neurotoxic effects of anthracycline- vs nonanthracycline-based chemotherapy on cognition in breast cancer survivors. *JAMA Oncology, 2*, 185–192. https://doi.org/10.1001/jamaoncol.2015.4333.

Kesler, S. R., Bennett, F. C., Mahaffey, M. L., & Spiegel, D. (2009). Regional brain activation during verbal declarative memory in metastatic breast cancer. *Clinical Cancer Research, 15*, 6665–6673. https://doi.org/10.1158/1078-0432.CCR-09-1227.

Kesler, S. R., Kent, J. S., & O'Hara, R. (2011). Prefrontal cortex and executive function impairments in primary breast cancer. *Archives of Neurology, 68*(11), 1447–1453.

Kesler, S., Hadi Hosseini, S. M., Heckler, C., Janelsins, M., Palesh, O., Mustian, K., & Morrow, G. (2013a). Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clinical Breast Cancer, 13*, 299–306. https://doi.org/10.1016/j.clbc.2013.02.004.

Kesler, S., Janelsins, M., Koovakkattu, D., Palesh, O., Mustian, K., Morrow, G., et al. (2013b). Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. *Brain Behavior and Immunity, 30*(Suppl3), S109–S116. https://doi.org/10.1016/j.bbi.2012.05.017.

Kesler, S. R., Watson, C. L., & Blayney, D. W. (2015). Brain network alterations and vulnerability to simulated neurodegeneration in breast cancer. *Neurobiology of Aging, 36*, 2429–2442. https://doi.org/10.1016/j.neurobiolaging.2015.04.015.

Kesler, S. R., Adams, M., Packer, M., Rao, V., Henneghan, A. M., Blayney, D. W., & Palesh, O. (2017a). Disrupted brain network functional dynamics and hyper- correlation of structural and functional connectome topology in patients with breast cancer prior to treatment. *Brain and Behavior: A Cognitive Neuroscience Perspective, 7*, e00643. https://doi.org/10.1002/brb3.643.

Kesler, S. R., Rao, A., Blayney, D. W., Oakley-Girvan, I. A., Karuturi, M., & Palesh, O. (2017b). Predicting long-term cognitive outcome following breast cancer with pre-treatment resting state fMRI and random forest machine learning. *Frontiers in Human Neuroscience, 11*, 555. https://doi.org/10.3389/fnhum.2017.00555.

Koch, M. (2018). Artificial intelligence is becoming natural. *Cell, 173*(3), 531–533. https://doi.org/10.1016/j.cell.2018.04.007.

Koppelmans, V., de Ruiter, M. B., van der Lijn, F., Boogerd, W., Seynaeve, C., van der Lugt, A., Vrooman, H., Niessen, W. J., Breteler, M. M. B., & Schagen, S. B. (2012). Global and focal brain volume in long-term breast cancer survivors exposed to adjuvant chemotherapy. *Breast Cancer Research and Treatment, 132*, 1099–1106. https://doi.org/10.1007/s10549-011-1888-1.

Koppelmans, V., de Groot, M., de Ruiter, M. B., Boogerd, W., Seynaeve, C., Vernooij, M. W., Niessen, W. J., Schagen, S. B., & Breteler, M. M. B. (2014). Global and focal white matter integrity in breast cancer survivors 20 years after adjuvant chemotherapy. *Human Brain Mapping, 35*, 889–899. https://doi.org/10.1002/hbm.22221.

Koppelmans, V., Vernooij, M. W., Boogerd, W., Seynaeve, C., Ikram, M. A., Breteler, M. M., et al. (2015). Prevalence of cerebral small-vessel disease in long-term breast cancer survivors exposed to both adjuvant radiotherapy and chemotherapy. *Journal of Clinical Oncology, 33*, 588–593. https://doi.org/10.1200/JCO.2014.56.8345.

Lee, M. H., Smyser, C. D., & Shimony, J. S. (2013). Resting-state fMRI: a review of methods and clinical applications. *AJNR. American Journal of Neuroradiology, 34*, 1866–1872. https://doi.org/10.3174/ajnr.A3263.

Lepage, C., Smith, A. M., Moreau, J., Barlow-Krelina, E., Wallis, N., Collins, B., MacKenzie, J., & Scherling, C. (2014). A prospective study of grey matter and cognitive function alterations in chemotherapy-treated breast cancer patients. *Springerplus., 3*, 444–454. https://doi.org/10.1186/2193-1801-3-444.

Li, X., Chen, H., Lv, Y., Chao, H. H., Gong, L., Li, C. R., et al. (2018). Diminished gray matter density mediates chemotherapy dosagerelated cognitive impairment in breast cancer patients. *Scientific Reports, 8*(1), 13801. https://doi.org/10.1038/s41598-018-32257-w.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature., 412*, 150–157. https://doi.org/10.1038/35084005.

López Zunini, R. A., Scherling, C., Wallis, N., Collins, B., MacKenzie, J., Bielajew, C., & Smith, A. M. (2013). Differences in verbal memory retrieval in breast cancer chemotherapy patients compared to healthy controls: a prospective fMRI study. *Brain Imaging and Behavior, 7*, 460–477. https://doi.org/10.1007/s11682-012-9213-0.

Mandelblatt, J. S., Stern, R. A., Luta, G., McGuckin, M., Clapp, J. D., Hurria, A., Jacobsen, P. B., Faul, L. A., Isaacs, C., Denduluri, N., Gavett, B., Traina, T. A., Johnson, P., Silliman, R. A., Turner, R. S., Howard, D., van Meter, J. W., Saykin, A., & Ahles, T. (2014). Cognitive impairment in older patients with breast cancer before systemic therapy: is there an interaction between cancer and comorbidity? *Journal of Clinical Oncology, 32*, 1909–1918. https://doi.org/10.1200/JCO.2013.54.2050.

McDonald, B. C., Conroy, S. K., Ahles, T. A., West, J. D., & Saykin, A. J. (2010). Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. *Breast Cancer Research and Treatment, 123*, 819–828. https://doi.org/10.1007/s10549-010-1088-4.

McDonald, B. C., Conroy, S. K., Ahles, T. A., West, J. D., & Saykin, A. J. (2012a). Alterations in brain activation during working memory processing associated with breast cancer and treatment: a prospective functional magnetic resonance imaging study. *Journal of Clinical Oncology, 30*, 2500–2508. https://doi.org/10.1200/JCO.2011.38.5674.

McDonald, B. C., Conroy, S. K., Smith, D. J., West, J. D., & Saykin, A. J. (2012b). Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. *Brain Behavior, and Immunity, 30*(Suppl), S117–S125. https://doi.org/10.1016/j.bbi.2012.05.007.

Menning, S., de Ruiter, M. B., Veltman, D. J., Koppelmans, V., Kirschbaum, C., Boogerd, W., Reneman, L., & Schagen, S. B. (2015). Multimodal MRI and cognitive function in patients with breast cancer prior to adjuvant treatment-the role of fatigue. *Neuroimage Clinical, 7*, 547–554. https://doi.org/10.1016/j.nicl.2015.02.005.

Menning, S., De, M. R., Veltman, D. J., Boogerd, W., Oldenburg, H. S., Reneman, L., et al. (2017). Changes in brain activation in breast cancer patients depend on cognitive domain and treatment type. *PLoS One, 12*(3), e0171724. https://doi.org/10.1371/journal.pone.0171724.

Meyers, C. A. (2008). How chemotherapy damages the central nervous system. *Journal of Biology, 7*, 11–13. https://doi.org/10.1186/jbiol73.

Miao, H., Chen, X., Yan, Y., He, X., Hu, S., Kong, J., Wu, M., Wei, Y., Zhou, Y., Wang, L., Wang, K., & Qiu, B. (2016). Functional connectivity change of brain default mode network in breast cancer patients after chemotherapy. *Neuroradiology, 58*, 1–8. https://doi.org/10.1007/s00234-016-1708-8.

Mo, C., Lin, H., Fu, F., Lin, L., Jie, Z., Meng, H., et al. (2017). Chemotherapy-induced changes of cerebral activity in resting-state functional magnetic resonance imaging and cerebral white matter in diffusion tensor imaging. *Oncotarget, 8*(46), 81273–81284. https://doi.org/10.18632/oncotarget.18111.

Nudelman, K. N. H., Wang, Y., Mcdonald, B. C., Conroy, S. K., Smith, D. J., West, J. D., et al. (2014). Altered cerebral blood flow one month after systemic chemotherapy for breast cancer: a prospective study using pulsed arterial spin labeling mri perfusion. *PLoS One, 9*, e96713. https://doi.org/10.1371/journal.pone.0096713.

Nudelman, K. N., Mcdonald, B. C., Wang, Y., Smith, D. J., West, J. D., O'Neill, D. P., et al. (2016). Cerebral perfusion and gray matter changes associated with chemotherapy-induced peripheral neuropathy. *Journal of Clinical Oncology, 34*, 677–683. https://doi.org/10.1200/JCO.2015.62.1276.

Piccirillo, J. F., Hardin, F. M., Nicklaus, J., Kallogjeri, D., Wilson, M., Ma, C. X., Coalson, R. S., Shimony, J., & Schlaggar, B. L. (2015). Cognitive impairment after chemotherapy related to atypical network architecture for executive control. *Oncology., 88*, 360–368. https://doi.org/10.1159/000370117.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di, C. G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology, 201*, 637–648. https://doi.org/10.1148/radiology.201.3.8939209.

Pomykala, K. L., de Ruiter, M. B., Deprez, S., Mcdonald, B. C., & Silverman, D. H. (2013). Integrating imaging findings in evaluating the post-chemotherapy brain. *Brain Imaging and Behavior, 7*, 436–452. https://doi.org/10.1007/s11682-013-9239-y.

Raichle, M. E. (2012). The restless brain. *Brain Connectivity, 1*, 3–12. https://doi.org/10.1089/brain.2011.0019.

Reisberg, B., Franssen, E. H., Hasan, S. M., Monteiro, I., Boksay, I., Souren, L. E. M., et al. (1999). Retrogenesis: clinical, physiologic, and pathologic mechanisms in brain aging, alzheimer's and other dementing processes. *European Archives of Psychiatry and Clinical Neuroscience, 249*(Suppl), 28–36.

Rick, O., Reußborst, M., Dauelsberg, T., Hass, H. G., König, V., Caspari, R., et al. (2018). Neurocog FX study: a multicenter cohort study on cognitive dysfunction in patients with early breast cancer. *Psycho-Oncology, 27*(1), 2016–2022. https://doi.org/10.1002/pon.4763.

Rudie, J. D., Brown, J. A., Beck-Pancer, D., Hernandez, L. M., Dennis, E. L., Thompson, P. M., Bookheimer, S. Y., & Dapretto, M. (2012). Altered functional and structural brain network organization in autism. *NeuroImage Clinical, 2*, 79–94. https://doi.org/10.1016/j.nicl.2012.11.006.

Sato, C., Sekiguchi, A., Kawai, M., Kotozaki, Y., Rui, N., Tada, H., et al. (2015). Postoperative structural brain changes and cognitive dysfunction in patients with breast cancer. *PLoS One, 10*(11), e0140655. https://doi.org/10.1371/journal.pone.0140655.

Scherling, C., Collins, B., Mackenzie, J., Bielajew, C., & Smith, A. (2011). Pre-chemotherapy differences in visuospatial working memory in breast cancer patients compared to controls: an fmri study. *Frontiers in Human Neuroscience, 5*, 122. https://doi.org/10.3389/fnhum.2011.00122.

Scherling, C., Collins, B., Mackenzie, J., Bielajew, C., & Smith, A. (2012). Prechemotherapy differences in response inhibition in breast cancer patients compared to controls: a functional magnetic resonance imaging study. *Journal of Clinical and Experimental Neuropsychology, 34*, 543–560. https://doi.org/10.1080/13803395.2012.666227.

Seigers, R., Schagen, S. B., Van, T. O., & Dietrich, J. (2013). Chemotherapy-related cognitive dysfunction: current animal studies and future directions. *Brain Imaging and Behavior, 7*(4), 453–459. https://doi.org/10.1007/s11682-013-9250-3.

Simóm, M., Rifà-Ros, X., Rodriguez-Fornells, A., & Bruna, J. (2013). Chemobrain: a systematic review of structural and functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 37*, 1311–1321. https://doi.org/10.1016/j.neubiorev.2013.04.015.

Smith, D. V., Utevsky, A. V., Bland, A. R., Nathan, C., Clithero, J. A., Harsch, A. E. W., et al. (2014). Characterizing individual differences in functional connectivity using dual-regression and seed-based approaches. *Neuroimage., 95*, 1–12. https://doi.org/10.1016/j.neuroimage.2014.03.042.

Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., et al. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage., 26*, 132–140. https://doi.org/10.1016/j.neuroimage.2005.01.028.

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues in Clinical Neuroscience, 15*, 247–262 PMCID: PMC3811098.

Stouten-Kemperman, M. M., De Ruiter, M. B., Caan, M. W. A., Boogerd, W., Kerst, M. J., Reneman, L., et al. (2015). Lower cognitive performance and white matter changes in testicular cancer survivors 10 years after chemotherapy. *Human Brain Mapping, 36*(11), 4638–4647. https://doi.org/10.1002/hbm.22942.

Sun, J., Tong, S., & Yang, G. Y. (2012). Reorganization of brain networks in aging and age-related diseases. *Aging and Disease, 3*, 181–193 PMCID: PMC3377830.

Tao, L., Lin, H., Yan, Y., Xu, X., Wang, L., Zhang, J., et al. (2016). Impairment of the executive function in breast cancer patients receiving chemotherapy treatment: a functional mri study. *European Journal of Cancer Care, 26*(6).

Valentini, A., Finch, A., Lubiński, J., Byrski, T., Ghadirian, P., Kimsing, C., et al. (2013). Chemotherapy-induced amenorrhea in patients with breast cancer with a brca1 or brca2 mutation. *Journal of Clinical Oncology, 31*, 3914–3919. https://doi.org/10.1200/JCO.2012.47.7893.

Vazquez, A. L., & Noll, D. C. (1998). Nonlinear aspects of the BOLD response in functional MRI. *Neuroimage, 7*, 108–118. https://doi.org/10.1006/nimg.1997.0316.

Wang, Y., Saykin, A. J., Pfeuffer, J., Lin, C., Mosier, K. M., Shen, L., Kim, S., & Hutchins, G. D. (2011). Regional reproducibility of pulsed arterial spin labeling perfusion imaging at 3t. *Neuroimage, 54*, 1188–1195. https://doi.org/10.1016/j.neuroimage.2010.08.043.

Wefel, J. S., Kesler, S. R., Noll, K. R., & Schagen, S. B. (2015). Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA: a Cancer Journal for Clinicians, 65*, 123–138. https://doi.org/10.3322/caac.21258.

Wu, X., Lv, X. F., Zhang, Y. L., Wu, H. W., Cai, P. Q., Qiu, Y. W., Zhang, X. L., & Jiang, G. H. (2015). Cortical signature of patients with HBV-related cirrhosis without overt hepatic encephalopathy: a morphometric analysis. *Frontiers in Neuroanatomy, 9*, 82. https://doi.org/10.3389/fnana.2015.00082.

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fmri data analysis. *Neuroimage, 22*, 394–400. https://doi.org/10.1016/j.neuroimage.2003.12.030.

Zang, Y. F., He, Y., Zhu, C. Z., Cao, Q. J., Sui, M. Q., Liang, M., et al. (2007). Altered baseline brain activity in children with adhd revealed by resting-state functional mri. *Brain & Development, 29*, 83–91. https://doi.org/10.1016/j.braindev.2006.07.002.

Zhang, X. D., & Zhang, L. J. (2018). Multimodal MR imaging in hepatic encephalopathy: state of the art. *Metabolic Brain Disease, 33*(3), 1–11. https://doi.org/10.1007/s11011-018-0191-9.

Zhang, L. J., Wu, S., Ren, J., & Lu, G. M. (2014). Resting-state functional magnetic resonance imaging in hepatic encephalopathy: current status and perspectives. *Metabolic Brain Disease, 29*, 569–582. https://doi.org/10.1007/s11011-014-9504-9.

Zou, Q. H., Zhu, C. Z., Yang, Y., Zuo, X. N., Long, X. Y., Cao, Q. J., Wang, Y. F., & Zang, Y. F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (alff) for resting-state fMRI: fractional alff. *Journal of Neuroscience Methods, 172*, 137–141. https://doi.org/10.1016/j.jneumeth.2008.04.012.